IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	§	
Donald MORTON	§	
Rishab K. GUPTA	§	
David M. EUHUS	§	
	§	Group Art Unit: 1802
Serial No. 07/431,533	§	
	§	Examiner: H. Sidberry
Filed: November 3, 1989	§	
	§	Atty Dkt.: CADL:002/PAR
For: URINARY TUMOR ASSOCIATED ANTIGEN, ANTIGENIC SUB-UNITS AND METHODS OF DETECTION	§	

BRIEF ON APPEAL

CERTIFICATE OF MAILING
37 C.F.R. 1.8

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Date

Steven L. Highlander

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BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the Office Action mailed on March 13, 1997. This brief is due on August 16, 1997, by virtue of the Notice of Appeal received on June 16, 1997. Also included with this filing is the fee for the brief. Should appellants' check be missing or deemed deficient, the Commissioner is authorized to deduct said fees from Arnold, White & Durkee Deposit Account No. 01-2508/CADL:002/HYL.

I. STATUS OF THE CLAIMS

Claims 1-46 were filed with the original application. Claims 47-79 have been added, and claims 1-18 and 20-61 have been canceled. Thus, claims 19 and 62-79 are pending in the application and are appealed. A copy of these claims is attached as Appendix 1.

II. STATUS OF THE AMENDMENTS

Amendments are offered with this brief that correct minor claim dependency problems that only recently were discovered. Entry of these amendments is believed proper given that no new issues are raised.

III. REAL PARTY IN INTEREST

This application has been assigned to Cancer Diagnostic Laboratories.

IV. RELATED APPEALS AND INTERFERENCES

There are no pending appeals or interferences for related cases.

V. SUMMARY OF THE INVENTION

The present invention relates to antigen compositions comprising purified urinary tumor associated antigen (U-TAA) and methods for their use in stimulating immune responses.

VI. ISSUES PRESENTED

(i) Is claim 72 enabled?

(ii) Is claims 62 anticipated by Real *et al.* (Exhibit A)?

(iii) Are claims 19, 62, 65, 67, 68, 71 and 73-79 unpatentable over Euhus *et al.* (Exhibit B)?

(iv) Are claims 63, 64, 66, 69 and 70 rejected?

VII. GROUPING OF THE CLAIMS

The claims do not stand or fall together. Separate grounds for patentability of various claims are set out below in §IX.

VIII. SUMMARY OF THE ARGUMENT

The examiner has rejected claim 72 under 35 U.S.C. §112, first paragraph soley on the grounds that the 2- to 5-fold increase in response set forth in the claim is not enabled because the data were generated with whole cells and the claim recites U-TAA. This position is based on mere speculation and, moreover, flies in the face (i) of scientific principles, which show that increases in dose correlate with increased response, and (ii) of scientific data that suggests otherwise.

The examiner maintains the rejection of claim 62 over Real *et al.* under 35 U.S.C. §102. Essentially, the examiner argues that the similar molecular weights makes these two tumor markers indistinguishable. However, a plethora of other characteristics, including tissue distribution and heat stability, renders this rejection more than suspect enough to defeat the rejection.

Finally, the examiner rejects claims 62 (anticipated) and 19, 65, 67, 68, 71 and 73-79 (obvious) over Euhus *et al.* Appellants have repeatedly traversed the rejection on the grounds that the reference does not enable the production of purified U-TAA given the lack of information on (i) its structure, (ii)

its immunological profile (monoclonal antibody binding) or (iii) parameters for effecting the isolation of U-TAA from the disclosed starting materials. The mere disclosure by Euhus *et al.* of an antibody for U-TAA does not place that antibody, or U-TAA, in the hands of the public according to the present invention, and thus does not place the invention in the hands of the public, as required under §102. This view was supported by two declarations of Dr. Ralph Reisfeld, Head of the Department of Molecular Immunology at the Scripps Institute (Exhibits C and D).

The maintenance of the rejection further is improper to the extent that it relies on the instant specification and the ease with which various separation procedures can be employed. This ignores (i) the case law which precludes appellants' specification from being used against their own claims and (ii) the additional disclosure provided by the specification, ***not found in the abstract***, that breathes meaning and significance into the excerpted passage.

Importantly, the absence of a meaningful description of U-TAA, or an antibody that recognizes U-TAA, would preclude the skilled artisan from ***confirming*** that the work described by Euhus *et al.* had, in fact, been reproduced. Without the ability to confirm the results, the enablement provided by the Euhus *et al.* disclosure is nil, and certainly does not arise to the level necessary to anticipate the present invention.

Turning to each of the dependent claims, which are rejected as obvious, appellants again submit that the rejections are improper. Each of these rejections is based on the premise that U-

TAA is available to the skilled artisan. As pointed out above, however, this is not the case. Thus, each of the rejections against claims 19, 65, 67, 68, 71 and 73-79 must fall as well.

IX. ARGUMENT

A. *Rejection Under 35 U.S.C. §112, First Paragraph*

The examiner has maintained the rejection of claim 72 as not supported by the specification. Specifically, the examiner argues that it is "not predictable" that appellants can achieve the recited 2- to 5-fold increase in anti-U-TAA titer, exemplified with whole cells, with purified antigen. Appellants respectfully traverse the rejection.

The examiner's only "reason" for the rejection is that the inclusion of other determinants in whole cells prevents extrapolation to the use of purified U-TAA. First, appellants submit that the examiner has not established that other determinants ***will*** affect the anti-U-TAA titer. Rather, the examiner merely has ***surmised*** that the inclusion of ancillary antigens ***may*** alter the subject's response. This sort of speculation, not based on any relevant evidence, is not sufficient to establish a *prima facie* case of non-enablement.

And even if this hypothesizing was correct, it would not mean that one could not readily achieve the response set forth in the claim. For example, by altering the ***amount*** of antigen presented to the subject, one can change the magnitude of an immune response. Similarly, routes of administration and repeat dosings permit one to alter responses as well. Thus, even if it were

true that one would expect differences between free antigen and whole cells, this would not prevent the recited result.

Moreover, appellants have published data that indicate purified U-TAA can, in fact, induce an immune response in animals. Hunt *et al.* (1992; Exhibit E) administered U-TAA to baboons via intramuscular or intravenous routes to generate a polyclonal antisera. Responses were measured by ELISA and chromium release assay. The results clearly show that purified U-TAA was capable of generating a significant humoral immune response. Thus, actual data lend further credence to the claims and further undercut the examiner's position.

In any event, appellants submit that the burden remains on the examiner to establish that one would not believe that the recited goals could be achieved. *In re Angstadt*, 190 USPQ 214 (CCPA 1976). And there is no reason for appellants to go to the trouble of supporting their presumptively enabling disclosure when the examiner has not shifted the burden. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971). Further, examples are ***not*** required to establish sufficient support for claims under §112 so long as the invention may be practiced without undue experimentation. *In re Borkowski*, 164 USPQ 642 (CCPA 1970).

Thus, from both scientific and legal standpoints, appellants submit that the examiner has not established that claim 72 is not enabled by the instant specification. Therefore, the Board is respectfully requested to reverse the rejection.

B. Rejection over Real et al. Under 35 U.S.C. §102

The examiner has maintained the rejection of claim 62 as anticipated by Real *et al.* According to the examiner, the dependent claims are not rejected because they recite properties of U-TAA that distinguish the antigen of Real *et al.*, but that claim 62 remains indistinguishable from the teachings of the reference. Appellants again traverse.

The premise of this rejection is that the examiner has made out a *prima facie* case of identity between U-TAA and Real *et al.*'s antigen and, therefore, it is up to appellants to disprove this proposition. The examiner's entire alleged *prima facie* case is based, apparently, on two facts: (i) both Real *et al.*'s antigen and the reduced subunit of U-TAA exhibit a molecular weight of 90 kD, based on SDS-PAGE and (ii) both Real *et al.*'s antigen and U-TAA are present in tumors.

Despite the similarity in molecular weight, appellants submit that there are no other facts that indicate these two antigens are the same. In fact, there are numerous facts that suggest the contrary, not the least of which is the fact that Real *et al.*'s antigen was demonstrated to be present on but a few melanoma samples. U-TAA, on the other hand, is found in most melanomas, most sarcomas, most neuroblastomas and most lung cancers. It also is found in breast, colon, prostate and ovary tumors. Given this tremendous disparity in tissue distribution, it is respectfully submitted that the examiner's initial *prima facie* case is not well-grounded, and hence, the burden has not shifted to appellants' to prove that these two antigens are dissimilar. For this reason alone, the rejection is improper and should be reversed.

C. Rejection over Euhus et al. Under 35 U.S.C. §102/§103

The examiner has maintained the rejection of claims 62 (anticipated) and 19, 65, 67, 68, 71 and 73-79 (obvious) over Euhus *et al.* This reference is said to teach purification of U-TAA by various methods. Appellants have repeatedly traversed the rejection on the grounds that the reference does not enable the production of purified U-TAA given the lack of information on (i) its structure, (ii) its immunological profile (monoclonal antibody binding) or (iii) parameters for effecting the isolation of U-TAA from the disclosed starting materials. The examiner deems the disclosure sufficient, however, at least with respect to the latter, and hence the rejection is maintained.

It is well established that a reference must teach how to make and use the claimed invention, *i.e.*, must "enable" the claimed invention, for it to be a ***valid*** reference against the claims of an application. In *Paperless Accounting Inc. v. Bay Area Rapid Transit Sys.*, 231 U.S.P.Q. 649 (Fed. Cir. 1986), the PTO's reviewing court said that a "§ 102(b) reference 'must sufficiently describe the claimed invention to have placed the public in possession of it'.... '[E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling.'"

Turning to Euhus *et al.*, it is true that an antibody specific for U-TAA is disclosed and that a purified form of U-TAA is described. None of the foregoing is relevant, however, to the question of anticipation (or obviousness) of an invention relating to an antigen composition or methods of immunization therewith. As indicated, merely disclosing "an antibody for UTAA" or various separative techniques does not provide an enabling disclosure for the production of an antigen

composition according to the present invention, and thus does not place the invention in the hands of the public, as required under §102.

This view is supported by the declarations of Dr. Ralph Reisfeld, Head of the Department of Molecular Immunology at the Scripps Institute (Exhibits C and D). Dr. Reisfeld first states that the Euhus *et al.* abstract would not be enabling for U-TAA or for methods relating to the diagnosis of melanoma using U-TAA or U-TAA-specific antibodies. In particular, "key conditions such as the proper pH or ionic strength under which isolation was conducted are missing, as are the migration distances or retention times for gel or column purification." According to Dr. Reisfeld, the absence of these details prevents the reproducible isolation and purification of U-TAA.

In response, the examiner substituted her own view that the reference would, in fact, provide sufficient teachings. This is based upon the belief that (i) pH or ionic strength for elution from DEAE columns is not required because a salt gradient could be used and (ii) migration distance and retention time is not need in gel filtration given the disclosure of a 620 kD complex and the use of standards. These comments do not make any sense. First, ionic strength and salt conditions are the same - the question is ***what*** salt condition or ionic strength will result in elution of the antigen. As illustrated by the reference provided by the examiner, a salt gradient results in elution of different species at different ionic strengths, but which one contains U-TAA? Second, the gel filtration reference in Euhus *et al.* was part of a combined separative procedure including dye ligand fractionation, yet not mention is

made of the type of dye ligand or the elution mechanism. Thus, the mere reference of gel filtration and an ultimate size of 620 kD cannot be said to place U-TAA in the hands of the artisan of ordinary skill.

The maintenance of the rejection further is improper to the extent that it relies on the instant specification and the ease with which various separation procedures can be employed. This ignores (i) the case law which precludes appellants' specification from being used against their own claims and (ii) the additional disclosure provided by the specification, ***not found in the abstract***, that breathes meaning and significance into the excerpted passage. In short, the instant application, which is not prior art, is enabling, whereas the abstract is ***not*** enabling. These facts do not support a rejection of the former over the latter, as indicated in previous actions.

In his second declaration, Dr. Reisfeld provides an additional reason why the Euhus *et al.* abstract is not enabling for the claimed subject matter. As Dr. Reisfeld points out, the absence of a meaningful description of U-TAA, or an antibody that recognizes U-TAA, would preclude the skilled artisan from ***confirming*** that the work described by Euhus *et al.* had, in fact, been reproduced. In other words, how would the skilled artisan know whether he or she had achieved what Euhus *et al.* described? The answer, of course, is that that could not. Without the ability to confirm the results, the enablement provided by the Euhus *et al.* disclosure is nil, and certainly does not arise to the level necessary to anticipate the present invention. The antibody of the present application has been deposited and will be made available pursuant to 37 C.F.R. §1.801-9 as deemed necessary.

Turning to each of the dependent claims, which are rejected as obvious, appellants again submit that the rejections are improper. The examiner concludes that, since U-TAA is anticipated, the use of U-TAA in a method of inducing an immune response is obvious (claims 19 and 65). Claims 67, 68 and 71 are said to recite inherent properties of U-TAA Claims 73-79 are rejected as reciting U-TAA at various concentrations as part of a pharmaceutical composition. Each of these rejections is based on the premise that U-TAA is available to the skilled artisan. As pointed out above, however, this is not the case. Thus, each of the rejections against claims 19, 65, 67, 68, 71 and 73-79 must fall as well.

Appellants submit that, despite the disclosure of Euhus *et al.*, one of ordinary skill in the art could neither reproduce the present invention, nor confirm that its reproduction had been accomplished. Thus, it is respectfully submitted that Euhus *et al.* is not an enabling disclosure and, hence, cannot be held to anticipate any of the instant claims. Therefore, it is requested that the Board reverse this rejection as well.

claims are, in fact, allowable or if the examiner merely has failed to specify the particular grounds for rejection. If rejected, appellants submit that these claims all are separately patentable over the rejections of record. Clarification in the examiner's answer is respectfully requested.

X. SUMMARY AND CONCLUSION

In light of the foregoing amendments and remarks, it is respectfully submitted that the appealed claims are enabled and novel over the art of record. Therefore, reversal of all rejections under 35 U.S.C. §112, first paragraph, 35 U.S.C. §102 and 35 U.S.C. §103 is requested.

Respectfully submitted,

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APPENDIX 1: PENDING CLAIMS

19. A method for inducing or enhancing in a subject the production of antibodies reactive with UTAA comprising administering an effective amount of the antigen composition of claim 62.

62. An antigen composition comprising a substantially purified tumor antigen, wherein the tumor antigen is identified as comprising Urinary Tumor Associated Antigen (UTAA) subunit which, after reduction by ß-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis, exhibits a molecular weight of about 90 to 100 kD.

63. The antigen composition according to claim 62, wherein UTAA is purified at least about 100-fold over UTAA found in urine.

64. The antigen composition according to claim 62, wherein said UTAA is present as at least about 0.6% of total protein in said composition.

65. The method of claim 19, wherein said method comprises enhancing in a subject the production of antibodies reactive with UTAA.

66. The composition of claim 63, wherein said UTAA is purified 105-fold over UTAA found in urine.

67. The composition of claim 62, wherein said UTAA has an isoelectric point of about 6.1.

68. The composition of claim 62, wherein said UTAA is heat stable at 100°C.

69. The composition of claim 62, wherein said UTAA is about 95% free of immunoglobulin.

70. The composition of claim 62, wherein said UTAA is about 99.5% free of immunoglobulin.

71. The composition of claim 62, wherein said UTAA contains glycosidase-sensitive carbohydrates.

72. The method of claim 65, wherein the observed enhancement of antibody production is about 2- to 5-fold.

73. A pharmaceutical composition comprising (i) an antigen composition comprising a substantially purified tumor antigen, wherein the tumor antigen is identified as comprising Urinary Tumor Associated Antigen (UTAA) subunit which, after reduction by β-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis, exhibits a molecular weight of about 90 to 100 kD and (ii) a pharmaceutical buffer.

74. (Amended) The pharmaceutical composition of claim [74] 73, wherein said antigen composition is present as at least about 0.63 µg/ml of buffer.

75. (Amended) The pharmaceutical composition of claim [75] 74, wherein said antigen composition is present as at least about 1.4 μg/ml of buffer.

76. (Amended) The pharmaceutical composition of claim [76] 75, wherein said antigen composition is present as at least about 36 μg/ml of buffer.

77. (Amended) The pharmaceutical composition of claim [75] 76, wherein said antigen composition is present as at least about 40 μg/ml of buffer.

78. (Amended) The pharmaceutical composition of claim [75] 77, wherein said antigen composition is present as at least about 100 μg/ml of buffer.

79. (Amended) The pharmaceutical composition of claim [75] 78, wherein said antigen composition is present as at least about 200 μg/ml of buffer.

APPENDIX 2: EXHIBITS